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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,267	THOMSON, AXEL ANDREAS	
	Examiner	Art Unit	
	Julie Ha	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8, 18,19,21 and 24-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,18,19,21 and 24-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :----------.

DETAILED ACTION

Response to Election/Restriction filed on May 03, 2007 is acknowledged. Cancellation of claims 9-17, 20 and 22-23 and addition of new claims 24-29 filed with Preliminary amendment on March 17, 2005 is acknowledged. Claims 1-8, 18-19, 21, 24-29 are pending in this application.

Election/Restriction

1. Applicant's election with traverse of species GnRH agonist and prostate cancer in the reply filed on May 03, 2007 is acknowledged. The traversal is on the ground(s) that no lack of unity objection was raised during the international phase. Further, the Applicant argues that the several species are not so numerous as to constitute an undue burden. This is not found persuasive because National stage application under 371 does not follow the International practices but follow the US practices. MPEP states the following: An international application should relate to only one invention or, if there is more than one invention, the inclusion of those inventions in one international application is only permitted if all inventions are so linked as to form a single general inventive concept (PCT Rule 13.1). With respect to a group of inventions claimed in an international application, unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" is defined in PCT Rule 13.2 as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. (see

MPEP 1850). Further, the claimed agents are patentably independent and distinct due to their different structures and functions. Additionally, the proliferative diseases claimed are independent and distinct from each other since they are different types of cancers and involve different cells. For example, basal cell carcinoma is a type of skin cancer, while medulloblastoma is a type of brain tumor. Furthermore, the search for each of the inventions is not co-extensive particularly with regard to the literature search. Burden consists not only of specific searching of classes and subclasses, but also of searching multiple databases for foreign references and literature searches. Burden also resides in the examination of independent claim sets for clarity, enablement, and double patenting issues. Further, a reference that would anticipate the invention of one group would not necessarily anticipate or even make obvious another group. Finally, the consideration for patentability is different in each case. Thus, it would be an undue burden to examine all of the above inventions in one application and the restriction for examination purposes as indicated above is deemed proper.

The requirement is still deemed proper and is therefore made FINAL. Claims 1-8, 18-19, 21, 24-29 are examined on the merits in this office action.

Objection-Minor Informalities

2. The title is objected to because the title is too long. The title is limited to 2-7 words maximum. A new title is required that is clearly indicative of the invention to which the claims are directed.

3. The title is objected to because of spelling errors. The title states, "Inhibitors of the SHH signaling patway and a testosterone supressing agent..." The correct spelling should be "pathway" and "suppressing". The Applicants are requested to correct these errors.

4. The specification is objected to due to the following informalities:

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.
    (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Rejection-35 U.S.C. 112, 2nd

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1 and 24-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 1 recites "a method of protecting a patient from possible adverse effects of a treatment..." This phrase in context to adverse effects is indefinite. It is unclear what are considered to be "adverse effects". For example, different patients will consider different level of symptoms as an "adverse effect". This can include such things as rashes, sore muscles, dry mouths, headaches and so on.

8. Claim 24 recites "a method according to claim 1 wherein the SHH-signaling pathway is inhibited by the administration of cyclopamine or a derivative thereof to the patient." This phrase is unclear since claim 1 recites that "possible adverse effects of a treatment involving inhibition of the SHH-signaling pathway in the patient, comprising suppressing testosterone or its effect in the patient." However, it is unclear since claim 1 reads that suppressing testosterone or its effect in the patient would protect a patient from possible adverse effects AND not administration of cyclopamine. Therefore, it is unclear whether suppressing testosterone or its effect in the patient would protect a patient from possible adverse effects, or administration of cyclopamine is required for protecting a patient from possible adverse effects, or administration of cyclopamine suppresses testosterone.

9. Claim 1 recites the limitation "the" in "inhibition of the SHH-signaling". There is insufficient antecedent basis for this limitation in the claim.

Rejection-35 U.S.C. 112, 1st

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-8, 18-19, 21 and 24-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for ameliorating the basal cell carcinoma and suppressing the effects of testosterone in patients with glioblastoma, and regulating prostatic growth in vitro, does not reasonably provide enablement for treating all proliferative diseases in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature or the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are

weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention is drawn to a method of treating proliferative disease (prostate cancer) in a patient comprising inhibiting the SHH-signaling pathway by administration of cyclopamine and suppressing testosterone or its effect in the patient by administering GnRH agonist. Further, the invention is drawn to a method of protecting a patient from proliferative disease (prostate cancer) in a patient comprising inhibiting the SHH-signaling pathway and suppressing testosterone or its effect in the patient by administering GnRH agonist.

(2) The state of the prior art:

The Merck manual indicates that there are about 500 topics on "Proliferative diseases". For example, the Merck manual lists Diabetic Retinopathy, Nephritic and Nephrotic syndromes, Candidiasis, Severe Combined Immunodeficiency (SCID), Henoch-Schonlein Purpura (HSP), Periodontitis, Occupational Asthma, lung cancer, angiogenesis and other autoimmune diseases to name just a few (see Merck manual enclosed). The Merck manual indicates that fibrillary and immunotactoid glomerulopathies (Nephritic and Nephrotic syndrome) found in renal biopsies, occur equally in men and women and have been described in patients greater than or equal to 10 years of age. The mechanism is unknown, although deposition of immunoglobulin,

particularly IgG κ and γ light chains and complement, suggest immune system dysfunction (see Merck Manual, Nephritic and Nephrotic syndrome, Fibrillary and Immunotactoid Glomerulopathies). The Merck manual further indicates that the condition is usually slowly progressive with renal insufficiency, progressing to end-stage renal disease in 50% of patients by 2 to 4 years (see Merck manual, Nephritic and Nephrotic syndrome, Fibrillary and Immunotactoid Glomerulopathies). Further, the Merck manual indicates that the membranoproliferative glomerulonephritis is a group of immune-mediated disorders characterized histologically by glomerular basement membrane thickening and proliferative changes on light microscopy (see Merck manual, membranoproliferative glomerulonephritis). The diagnosis is by renal biopsy (see Merck manual, Diagnosis). Furthermore, the Merck manual indicates that the long-term prognosis is poor (see Merck manual, Prognosis and Treatment).

Gestational Trophoblastic Disease is another example of a proliferative disease. The Merck manual indicates that Gestational trophoblastic disease is proliferation of trophoblastic tissue in pregnant or recently pregnant women (see Merck manual, Gestational Trophoblastic Disease). The Merck manual indicates that vaginal bleeding, lack of fetal movement, absent fetal heart sounds, and severe vomiting are common. Passage of grapelike tissue strongly suggests the diagnosis and complications may include uterine infection, sepsis, hemorrhagic shock and preeclampsia, which may occur during early pregnancy (see Merck manual, Symptoms, Signs, and Diagnosis). Furthermore, the Merck manual indicates that hydatidiform mole, invasive mole, and placental site trophoblastic tumors are evacuated by suction curettage, and if

childbearing is not planned, hysterectomy may be done. Persistent disease is usually treated with chemotherapy (see Merck manual, Treatment).

Furthermore, the state of the art with respect to animal models indicates that xenograft mouse models are poor predictors of tumor behavior in humans. Van Weerden et al state that "in vivo models are essential for the study of the biological behavior of tumor tissue in its natural (organ) environment that cannot easily be mimicked in an in vitro setting. Important physiological processes that are lacking in vitro include three-dimensional structure, angiogenesis, stromal interaction influencing tumor development and tumor growth, and finally metastatic spread to other tissues" (see p. 267, right column, Discussion). Trisha Gura echoes similar sentiments in a *Science* article. The article indicates that the fundamental problem in cancer research is that model systems are not predictive of in-vivo activity (see page 1041 or p. 1 of enclosed printout, 2nd paragraph). The article goes on to state xenograft models in mice "don't behave like naturally occurring tumors in humans--they don't spread to other tissues." (See page 1041 or p. 2 or enclosed printout, 4th paragraph). Further, other systems such as clonogenic assays are not always helpful since they "can't always predict how a tumor will respond to a drug in an animal" and "[s]ometimes they don't work because the cells simply fail to divide in culture." (See page 1042 or p. 3 or printout, 7th paragraph). Further, the Jain article states that for solid tumors, the clinical results to date have not met the high expectation obtained as a result of in in-vitro testing (see the paragraph of page 1079-1080). "Even with the best animal model, however, we still need to better understand how the process of biodistribution of various

agents 'scales-up' from mouse to human. The biochemical and physiological differences between these species make this knowledge critical."

The art provide numerous proliferative diseases and provide guidance as how to alleviate some symptoms of proliferative diseases such as gestational trophoblastic disease, but since the types of diseases are numerous and types of treatments are different in different cases, the prior art does not provide how to determine individuals who are susceptible to certain proliferative diseases. However, none of the prior arts provide guidance as how to determine individuals who are susceptible to proliferative diseases.

(3) The relative skill of those in the art:

The relative skill of those in the art is high.

(4) The predictability or unpredictability of the art:

Applicant's activity is based on the determining the patient population that is susceptible to proliferative disease, the predictability is low. This is due to the fact that the art has recognized the numerous different proliferative diseases known in the medical field. For example, not all proliferative diseases involve suppressing testosterone in the patient. For example, as described above, The Merck manual indicates that fibrillary and immunotactoid glomerulopathies (Nephritic and Nephrotic syndrome) found in renal biopsies, occur equally in men and women and have been described in patients greater than or equal to 10 years of age. The mechanism is

unknown, although deposition of immunoglobulin, particularly IgG κ and γ light chains and complement, suggest immune system dysfunction (see Merck Manual, Nephritic and Nephrotic syndrome, Fibrillary and Immunotactoid Glomerulopathies). The Merck manual further indicates that the condition is usually slowly progressive with renal insufficiency, progressing to end-stage renal disease in 50% of patients by 2 to 4 years (see Merck manual, Nephritic and Nephrotic syndrome, Fibrillary and Immunotactoid Glomerulopathies). Further, the Merck manual indicates that the membranoproliferative glomerulonephritis is a group of immune-mediated disorders characterized histologically by glomerular basement membrane thickening and proliferative changes on light microscopy (see Merck manual, membranoproliferative glomerulonephritis). The diagnosis is by renal biopsy (see Merck manual, Diagnosis). Furthermore, the Merck manual indicates that the long-term prognosis is poor (see Merck manual, Prognosis and Treatment).

Additionally, the Merck manual indicates that Gestational trophoblastic disease is proliferation of trophoblastic tissue in pregnant or recently pregnant women (see Merck manual, Gestational Trophoblastic Disease). The Merck manual indicates that vaginal bleeding, lack of fetal movement, absent fetal heart sounds, and severe vomiting are common. Passage of grapelike tissue strongly suggests the diagnosis and complications may include uterine infection, sepsis, hemorrhagic shock and preeclampsia, which may occur during early pregnancy (see Merck manual, Symptoms, Signs, and Diagnosis). Furthermore, the Merck manual indicates that hydatidiform mole, invasive mole, and placental site trophoblastic tumors are evacuated by suction

curettage, and if childbearing is not planned, hysterectomy may be done. Persistent disease is usually treated with chemotherapy (see Merck manual, Treatment).

The claim doesn't identify the patient population, therefore, the claim implies that anyone can be protected against proliferative diseases. However, the Applicant has not shown who will be susceptible to proliferative disease. There are too many variables between the patient populations, thus, it clearly shows the unpredictability of the art.

(5) The breadth of the claims:

Claims 1 and dependent claims 24-29 are drawn to prevention of prostate cancer by inhibiting the SHH-signaling pathway by administering GnRH agonist. Claims 2 and dependent claims 3-8, 18-19 and 21 are drawn to a method of treating a prostate cancer in a patient wherein both GnRH agonist and cyclopamine are administered to the patient in need.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples:

Although the specification provides guidance on how to administer the compound, it is unclear as to when to administer the compound. The specification discloses that the sonic hedgehog regulates prostatic growth and epithelial differentiation (see Example 1) and the experimentation was performed on epithelial cells in a Petri dish in vitro. Furthermore, the specification discloses that male patients presenting with basal cell carcinoma is administered with leuprorelin (GnRH agonist)

(3.75 mg every four weeks intramuscularly) until castrate levels of testosterone are reached (0.5 ng/ml) and then the patient is administered cyclopamine (see Example 2). Further, the specification discloses that a male patient presenting with glioblastoma is administered flutamide (250 mg three times daily per os) to suppress the effects of testosterone, and then the patient is administered an inhibitor of the SHH-signaling pathway (see Example 3). However, there are no in vivo results that indicate Examples 2 and 3, thus there are not enough guidance useful in treating a patient with prostate cancer.

There are not enough working examples for guidance for treating a patient with prostate cancer. The specification discloses that the sonic hedgehog regulates prostatic growth and epithelial differentiation (see Example 1) and the experimentation was performed on epithelial cells in a Petri dish in vitro. As described above, the state of the art with respect to animal models indicates that xenograft mouse models are poor predictors of tumor behavior in humans. Van Weerden et al state that "in vivo models are essential for the study of the biological behavior of tumor tissue in its natural (organ) environment that cannot easily be mimicked in an in vitro setting. Important physiological processes that are lacking in vitro include three-dimensional structure, angiogenesis, stromal interaction influencing tumor development and tumor growth, and finally metastatic spread to other tissues" (see p. 267, right column, Discussion). Trisha Gura echoes similar sentiments in a *Science* article. The article indicates that the fundamental problem in cancer research is that model systems are not predictive of in-vivo activity (see page 1041 or p. 1 of enclosed printout, 2nd paragraph). The article

goes on to state xenograft models in mice "don't behave like naturally occurring tumors in humans--they don't spread to other tissues." (See page 1041 or p. 2 or enclosed printout, 4th paragraph). Further, other systems such as clonogenic assays are not always helpful since they "can't always predict how a tumor will respond to a drug in an animal" and "[s]ometimes they don't work because the cells simply fail to divide in culture." (See page 1042 or p. 3 or printout, 7th paragraph). Further, the Jain article states that for solid tumors, the clinical results to date have not met the high expectation obtained as a result of in in-vitro testing (see the paragraph of page 1079-1080). "Even with the best animal model, however, we still need to better understand how the process of biodistribution of various agents 'scales-up' from mouse to human. The biochemical and physiological differences between these species make this knowledge critical."

Furthermore, the claims are drawn to the treatment of all proliferative diseases. However, the specification has only shown effectiveness towards prostate cancer, basal cell carcinoma, and glioblastoma. It is well known that the all proliferative diseases such as cancers to not have the same mechanism of development and growth. Thus one could not assume that an agent effective against one tumor would be effective against all types of tumors. Moreover, animal models set forth for cancer are not good predictors of the efficacy in humans. As indicated in the state of the art with respect to cancer animal models, models in mice don't behave like naturally occurring tumors in humans--they don't spread to other tissues. In essence, the art indicates that "the fundamental problem in drug discovery for cancer is that the model systems are not

predictive at all." (See Science article on p. 1 of enclosed, 2nd paragraph). The cancer animal models and cell models, although provide valuable information for delivery of therapeutics, to not correlate to human in-vivo efficacy.

Additionally, as explained above, types of proliferative diseases are vast. The Merck manual lists 500 different proliferative diseases. The working example provided examples of basal cell carcinoma, glioblastoma (in patients) and prostatic cells in vitro. Additionally, the specification discloses that the sonic hedgehog (SHH)-signaling pathway regulates epithelial mesenchymal interactions during the development of many organs (see paragraph [0002]), it would be found in many organs in the body. Since there are vast number of proliferative diseases that would involve SHH-signaling pathway and suppressing testosterone or its effect in the patient,

The specification has not provided guidance in the way of a disclosure to how to determine individuals that need protection against proliferative diseases. The specification discloses administering the compound to basal cell carcinoma, glioblastoma and prostatic cells in vitro. Additionally, the specification discloses that the sonic hedgehog (SHH)-signaling pathway regulates epithelial mesenchymal interactions during the development of many organs (see paragraph [0002]), it would be found in many organs in the body. Since there are vast numbers of proliferative diseases that would involve SHH-signaling pathway and suppressing testosterone or its effect in the patient, there is not enough guidance in the way of a disclosure to determine the patient population in need of such protection and treatment. As described above, The Merck manual indicates that there are about 500 topics on "Proliferative diseases". For

example, the Merck manual lists Diabetic Retinopathy, Nephritic and Nephrotic syndromes, Candidiasis, Severe Combined Immunodeficiency (SCID), Henoch-Schonlein Purpura (HSP), Periodontitis, Occupational Asthma to name just a few (see Merck manual enclosed). The Merck manual indicates that fibrillary and immunotactoid glomerulopathies (Nephritic and Nephrotic syndrome) found in renal biopsies, occur equally in men and women and have been described in patients greater than or equal to 10 years of age. The mechanism is unknown, although deposition of immunoglobulin, particularly IgG κ and γ light chains and complement, suggest immune system dysfunction (see Merck Manual, Nephritic and Nephrotic syndrome, Fibrillary and Immunotactoid Glomerulopathies). The Merck manual further indicates that the condition is usually slowly progressive with renal insufficiency, progressing to end-stage renal disease in 50% of patients by 2 to 4 years (see Merck manual, Nephritic and Nephrotic syndrome, Fibrillary and Immunotactoid Glomerulopathies). Further, the Merck manual indicates that the membranoproliferative glomerulonephritis is a group of immune-mediated disorders characterized histologically by glomerular basement membrane thickening and proliferative changes on light microscopy (see Merck manual, membranoproliferative glomerulonephritis). The diagnosis is by renal biopsy (see Merck manual, Diagnosis). Furthermore, the Merck manual indicates that the long-term prognosis is poor (see Merck manual, Prognosis and Treatment).

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Gestational Trophoblastic Disease). The Merck manual indicates that vaginal bleeding, lack of fetal movement, absent fetal heart sounds, and severe vomiting are common. Passage of grapelike tissue strongly suggests the diagnosis and complications may include uterine infection, sepsis, hemorrhagic shock and preeclampsia, which may occur during early pregnancy (see Merck manual, Symptoms, Signs, and Diagnosis). Furthermore, the Merck manual indicates that hydatidiform mole, invasive mole, and placental site trophoblastic tumors are evacuated by suction curettage, and if childbearing is not planned, hysterectomy may be done. Persistent disease is usually treated with chemotherapy (see Merck manual, Treatment).

There is no clear guidance as to how to determine the patient population, since not all people suffering from proliferative diseases need suppression of testosterone. Since the prior art recognizes vast number of proliferative diseases, more guidance is necessary.

(8) The quantity of experimentation necessary:

Since it is uncertain to predict the patient population who are susceptible to proliferative diseases, and since different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine if the cyclopamine and GnRH agonist would be effective in slowing the growth rate of tumors in a subject having proliferative diseases, such as cancer.

Please note that the term "prevent" is an absolute definition which means to stop from occurring and, thus, requires a higher standard for enablement than does "therapeutic" or "treat" or "alleviate", especially since it is notoriously well accepted in the medical art that the vast majority of afflictions/disorders suffered by mankind cannot be totally prevented with current therapies (other than certain vaccination regimes)- including preventing such disorders as prostate cancer, which is clearly not recognized in the medical art as being totally preventable condition.

Rejection-35 U.S.C. 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1 and 25-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Walsh et al (US Patent # 5925619).

14. The instant claims are drawn to a method of protecting a patient from possible adverse effects of a treatment involving inhibition of the SHH-signaling pathway in the patient, the method comprising suppressing testosterone or its effect in the patient. The claims are further drawn to a method wherein testosterone or its effect is suppressed by administering GnRH agonist and wherein the proliferative disease is prostate cancer.

15. Walsh et al teach a pharmaceutical or veterinary formulation comprising deslorelin (a potent GnRH agonist) for the treatment of prostate and breast cancer and

other conditions in humans where suppression of testosterone or estradiol levels is beneficial (see abstract and column 2, lines 49-51). This reads on claims 1 and 25-29. Furthermore, the reference teaches that when the rods containing 6 mg of deslorelin were implanted into male and female dogs, and the results show that the formulation is able to suppress testosterone levels in dogs for 12 months (see column 5, lines 61-65). Since the reference disclose the same claimed disease to be treated, the same claimed active agent, the disclosed method of using GnRH agonist deslorelin would inherently suppress testosterone to castrate levels. Thus, the prior art meets the limitations of claims 1 and 25-29.

16. Claims 1 and 24-25 and 27-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Dudek et al (WO 02/030462).

17. The instant claims are drawn to a method of protecting a patient from possible adverse effects of a treatment involving inhibition of the SHH-signaling pathway in the patient, the method comprising suppressing testosterone or its effect in the patient, wherein the SHH-signaling pathway is inhibited and testosterone is suppressed by administration of cyclopamine, wherein the treatment is for prostate cancer in male patients.

18. Dudek et al (WO 02/030462) teach compositions and methods for inhibiting angiogenesis and treating or preventing unwanted cell proliferation, including tumors, by inhibiting the hedgehog pathway, with an antagonist of the hedgehog pathway, and list 7 compounds including cyclopamine (see abstract). The reference teaches that hedgehog signaling plays an important role in normal prostate development. Sonic

hedgehog is required for prostate growth, and expression of SHH is strongly correlated with prostate ductal branching. Furthermore, the reference discloses that recent evidence supporting the essential role of SHH in proper prostate branching demonstrates that treatment of embryonic prostate with hedgehog antagonist cyclopamine inhibits growth and branching (see p. 174, lines 4-9). This meets the limitation of claims 1, 24-25 and 27-29. Since the reference disclose the same claimed disease to be treated, the same claimed active agent, the disclosed method of using GnRH agonist cyclopamine would inherently suppress testosterone levels to castrate levels. Therefore, the prior art reads on claim 25. Furthermore, the reference discloses pharmaceutical preparations comprising as an active ingredient, a hedgehog antagonist or ptc agonist formulated in an amount sufficient to inhibit, in vivo, proliferation or other biological consequences of hedgehog gain-of-function (see p. 14, lines 29-30 and continued on p. 15, lines 1-2). Furthermore, the reference teaches that the subject treatments using hedgehog antagonists can be effective for both human and animal subjects (see p. 15, lines 3-4). This reads on claim 27, since the prior art teaches suppressing prostate growth and branching, the patients are male. Claim 1 is broadly interpreted as "a method of protecting a patient comprising suppressing testosterone or its effect in the patient". Thus, claim 24, wherein the administration of cyclopamine or a derivative thereof to the patient is read as: the agent that suppresses testosterone or its effect in the patient.

Rejection-35 U.S.C. 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

21. Claims 1 and 24-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dudek et al (WO 02/030462) in view of Walsh et al (US Patent # 5925619).

22. The instant claims are drawn to a method of protecting a patient from possible adverse effects of a treatment involving inhibition of the SHH-signaling pathway in the patient, the method comprising suppressing testosterone or its effect in the patient, wherein the SHH-signaling pathway is inhibited by the administration of cyclopamine and testosterone is suppressed by administration of GnRH agonist, wherein the treatment is for prostate cancer in male patients.

23. Dudek et al (WO 02/030462) teachings are described supra (see paragraph 18). The difference between the reference and the instant claims is that the reference does not teach suppression of testosterone by GnRH agonist.

24. However, as described supra, Walsh et al teach a pharmaceutical or veterinary formulation comprising deslorelin (a potent GnRH agonist) for the treatment of prostate and breast cancer and other conditions in humans where suppression of testosterone or estradiol levels is beneficial (see abstract and column 2, lines 49-51). Furthermore, the reference teaches that when the rods containing 6 mg of deslorelin were implanted into male and female dogs, and the results show that the formulation is able to suppress testosterone levels in dogs for 12 months (see column 5, lines 61-65).

25. Therefore, it would have been obvious of one of ordinary skill in the art to combine the two cyclopamine and GnRH agonist to treat prostate cancer because Dudek et al teach that cyclopamine is used to inhibit the growth and branching of prostate cancer, and Walsh et al teach that deslorelin (a potent GnRH agonist) for the treatment of prostate and breast cancer. Combining the two compounds for the treatment of the same disease would give an additive effect. One of ordinary skill in the art would be motivated to combine the two agonists together because each are individually used to treat prostate cancer.

26. The MPEP states the following: "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.). See also

In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and Ex parte Quadranti, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious). But see In re Geiger, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987) ("Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been prima facie obvious, within the meaning of 35 U.S.C. 103, to employ these components in combination for their known functions and to optimize the amount of each additive....Appellant argues... hindsight reconstruction or at best,... obvious to try'.... We agree with appellant."). In the instant case, since both agents are individually taught to treat prostate cancer, it would be obvious to form the third composition combining the two agents to be used in the treatment of prostate cancer. Therefore, there is a reasonable expectation of success to combine the two agents to have an additive effect once combined to be used for the treatment prostate cancer, since "[T]he idea of combining them flows logically from their having been individually taught in the prior art".

27. Claims 2-8, 18-19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walsh et al (US Patent # 5925619) as applied to claims 1 and 25-29

above, and further in view of Dudek et al (WO 02/030462) and Dudek et al (US Patent # 6291516).

28. The claims are drawn to a method of treating a proliferative disease (prostate cancer) in a patient the method comprising inhibiting the SHH-signaling pathway and suppressing testosterone or its effect in the patient. The claims are further drawn to a pharmaceutical composition comprising cyclopamine or a derivative thereof and GnRH agonist are administered to a patient in need thereof.

29. As described supra, Walsh et al teach a pharmaceutical or veterinary formulation comprising deslorelin (a potent GnRH agonist) for the treatment of prostate and breast cancer and other conditions in humans where suppression of testosterone or estradiol levels is beneficial (see abstract and column 2, lines 49-51). This reads on claims 1-2 and 4-8. Furthermore, the reference teaches that when the rods containing 6 mg of deslorelin were implanted into male and female dogs, and the results show that the formulation is able to suppress testosterone levels in dogs for 12 months (see column 5, lines 61-65). This meets the limitations of claims 2-8. The differences between the reference and the instant claims are that the reference does not teach cyclopamine and a pharmaceutically acceptable carrier.

30. However, Dudek et al (WO 02/030462) teach compositions and methods for inhibiting angiogenesis and treating or preventing unwanted cell proliferation, including tumors, by inhibiting the hedgehog pathway, with an antagonist of the hedgehog pathway, and list 7 compounds including cyclopamine (see abstract). The reference teaches that hedgehog signaling plays an important role in normal prostate

development. Sonic hedgehog is required for prostate growth, and expression of SHH is strongly correlated with prostate ductal branching. Furthermore, the reference discloses that recent evidence supporting the essential role of SHH in proper prostate branching demonstrates that treatment of embryonic prostate with hedgehog antagonist cyclopamine inhibits growth and branching (see p. 174, lines 4-9). Furthermore, the reference discloses pharmaceutical preparations comprising as an active ingredient, a hedgehog antagonist or ptc agonist formulated in an amount sufficient to inhibit, in vivo, proliferation or other biological consequences of hedgehog gain-of-function (see p. 14, lines 29-30 and continued on p. 15, lines 1-2). Furthermore, the reference teaches that the subject treatments using hedgehog antagonists can be effective for both human and animal subjects (see p. 15, lines 3-4).

31. Furthermore, Dudek et al (US Patent # 6291516) teach the pharmaceutical composition comprising small molecule such as cyclopamine, can be formulated for administration with a biologically acceptable and/or sterile medium, such as water, buffered saline, polyol or suitable mixtures thereof (see column 53, lines 18-23) and these compound may be administered to humans and other animals for therapy by any suitable route of administration (see column 54, lines 13-15) and that pharmaceutically acceptable carriers such as vehicle, liquid or solid filler, diluent, excipient, solvent or encapsulating materials can be utilized to carry or transport the subject regulators from one organ or portion of the body to another (see column 55, lines 55-61). Furthermore, Dudek et al teach methods and reagents for inhibiting aberrant growth states resulting from hedgehog gain-of-function, ptc loss-of-function or smoothened gain-of-function

comprising contacting a cell with a compound (cyclopamine included in Fig. 1) in an amount sufficient to control the aberrant growth state (see abstract).

32. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Walsh et al and Dudek et al since both teach the treatment of proliferative disease, prostate cancer using GnRH agonist (Walsh) and cyclopamine (Dudek). Furthermore, Dudek et al (US Patent '516) teach that pharmaceutically acceptable carriers can be utilized to carry or transport the subject regulators from one organ or portion of the body to another (see column 55, lines 55-61). One of ordinary skill in the art would be motivated to combine, since combining the two compounds in conjunction with a pharmaceutically acceptable carrier for the treatment of the same disease would give an additive effect.

33. Furthermore, the MPEP states the following: "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.). See also In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in

cast iron.); and Ex parte Quadranti, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious). But see In re Geiger, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987) ("Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been prima facie obvious, within the meaning of 35 U.S.C. 103, to employ these components in combination for their known functions and to optimize the amount of each additive....Appellant argues... hindsight reconstruction or at best,... obvious to try'.... We agree with appellant."). In the instant case, since both agents are individually taught to treat prostate cancer, it would be obvious to form the third composition combining the two agents to be used in the treatment of prostate cancer. Therefore, there is a reasonable expectation of success to combine the two agents along with a pharmaceutically acceptable carriers, to have an additive effect once combined and to carry or transport the subject regulators from one organ or portion of the body to another, for the treatment prostate cancer, since "[T]he idea of combining them flows logically from their having been individually taught in the prior art".

Conclusion

34. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Ha whose telephone number is 571-272-5982. The examiner can normally be reached on Mon-Fri, 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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